Clinical Pharmacology & Biopharmaceutics

Commentary Open Access

Goodbye, Neuroleptic Malignant Syndrome?

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Keywords: Antipsychotics; Muscarinic; Neuroleptic malignant syndrome; Xanomeline

Introduction

Neuroleptic malignant syndrome (NMS) has been reported with the routine use of all available antipsychotic agents. Its fatality rate may be as high as 11.6% of cases [1], and patients who recover yet develop indefinite neuropsychiatric sequalae have been described. It most commonly results from the use of dopamine-receptor antagonists, however, NMS may rarely occur after the rapid withdrawal of dopaminergic medications typically used for Parkinson's. Similar to NMS is the very rare syndrome of malignant hyperpyrexia with antipsychotic agents, which is indistinguishable in the acute setting from rapidly progressive NMS.

The clinical presentation of mental status changes, fever, extreme muscle rigidity with elevated creatine phosphokinase (CPK), and autonomic instability, are classic and diagnostic of NMS, however, subclinical variants may occur, involving limited symptoms, a much less likelihood of fatality or sequelae, and a resolution of symptoms with discontinuation of the offending agent.

A concern with the use of long-acting injectable antipsychotics has been the possibility that if NMS occurs, the syndrome may be prolonged or even unresolvable with standard supportive measures or electroconvulsive therapy, as the ongoing release of the offending agent may be present for days, weeks, or even several months depending on the preparation used. Yet data thus far, most of which was gathered prior to six-month-duration LAI availability, indicates the rates of occurrence and the rates of fatality are no different than oral agents [2].

The mechanism of NMS has yet to be fully elaborated but is believed to result from a rapid and significant reduction in central dopaminergic activity. This change is thought to result in the clinical manifestations of rigidity, hyperthermia, and mental status changes. In one case report, imaging studies confirmed a complete lack of D2 binding during the acute phase of NMS [3]. Further, another study demonstrated consistency low CNS levels of homovanillic acid (a dopamine metabolite) in patients with acute NMS [4].

Case reports of NMS involving non-antipsychotic agents are consistent as far as the offending agent possessing some component of dopaminergic activity, such as metoclopramide, promethazine, bupropion, and donepezil [5]. Some agents may heighten the risk when added to antipsychotic therapy, such as lithium, valproic acid, and certain drugs of abuse, particularly stimulants. A lesser-known risk factor is low plasma iron levels [6], and dehydration is a finding in 92% of NMS cases [7].

The efficacy of dopamine postsynaptic blockade for positive symptoms led to the dopamine hypothesis of schizophrenia and over 70 years of agents that target dopamine receptors, at least as a component of their activity. The newer muscarinic hypothesis informs that muscarinic receptors are highly expressed in the mesolimbic system, the dysfunction of which is associated with psychosis, and further, the interplay of all pathways in this system may be more fundamental to disease state than isolating a single receptor type.

Of the five known muscarinic receptors, M1 and M4 have been identified as possibly contributory in schizophrenia. Three clinical trials of xanomeline (a dual muscarinic-1 and muscarinc-4 receptor agonist with no direct dopamine-blocking activity), combined with trospium chloride (a peripherally-restricted muscarinic antagonist), have shown efficacy in schizophrenia, significantly reducing Positive and Negative Syndrome Scale total scores. When further examining the data, the Positive Symptom Subscale was also reduced significantly when compared with placebo, eliminating the criticism of some newer agents,that are noted in clinical trials to lower PANSS scores without affecting positive symptoms in a clinically meaningful way. All three short-term studies of xanomeline-trospium have been published and are remarkable for the absence of any dopaminergic-related side effects or adverse events [8,9].

Emraclidine is described as a highly selective at the M4 receptor, acting as a "positive allosteric modulator," i.e., increasing agonist activity at M4. This receptor subtype is selectively expressed in the striatum and is believed key in regulating acetylcholine and dopamine activity. M4 activation will regulate dopamine levels indirectly, again, without directly blocking dopamine receptors. Like xanolamine, this compound is known to lower dopamine activity without the risk of side effects associated with dopamine receptor blockade. Phase II trials have shown tolerability thus far, and as expected, an absence of traditional motor side effects (extrapyramidal symptoms and tardive dyskinesia) that may occur with available antipsychotics [10].

We also have data from phase I clinical trials of ML-007, another M1/M4 receptor agonist. Thus far, it too has been shown to be safe and well tolerated. In fact, when administered with a muscarinic antagonist, the plasma ML-007 concentrations reached twelve times the minimum plasma target concentration, and this high circulating amount was not only well tolerated, but an intolerable dose was unable to be identified [11].

Other compounds in development include NBI-1117568 (an M4 selective agonist in Phase 2 trials), NBI-1117570 (an M1/M4 selective dual agonist in Phase 1 trials), NBI-1117569 (an M4-preferring agonist in Phase 1), and NBI-111756 (a unique M1-preferring agonist expected to soon enter Phase 1 trials).

In summary, we will soon have the possibility of reducing central dopaminergic transmission without direct dopamine receptor activity,

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Received: 27-July-2024, Manuscript No: cpb-24-143353, **Editor Assigned:** 30-July-2024, Pre QC No cpb-24-143353 (PQ), **Reviewed:** 16-August -2024, QC No: cpb-24-143353, **Revised:** 19-August-2024, Manuscript No: cpb-24-143353 (R), **Published:** 26-August-2024, DOI: 10.4172/2167-065X.1000478

Citation: Andrew F (2024) Goodbye, Neuroleptic Malignant Syndrome? Clin Pharmacol Biopharm, 13: 478.

and thus, the possible absence of side effects and adverse events traditionally associated with direct D2 blockade. Thus, we have a new class of agents that may possess no risk of NMS based on all currently known mechanisms of this potentially fatal adverse event.

In three clinical trials, no xanomeline patients experienced NMS. The main side effects were gastrointestinal, noted to be generally transient and mild or moderate in severity. Patients will still be warned about the possibility of NMS due to the class concern, yet over time, we may be able to completely subtract this concern from the new category of atypical, muscarinic-based antipsychotics.

Because the unique mechanism of M1/M4 antipsychotics may lend them to safe combination therapy with traditional agents, we must be vigilant to note whether NMS occurs in this context, as opposed to monotherapy with muscarinic agents. Based on our knowledge of the mechanism of NMS, we anticipate that NMS will be likely be a null concern with this new class of agents.

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